REMARKS

Applicants have fully considered the Final Office Action mailed December 1, 2005. In view of the Remarks and Arguments presented below, Applicants request reconsideration of the application.

The Office Action

In the Final Office Action, the Examiner entered the amendments to claims 33-36, 54, and 67-68. The Examiner noted that priority documents were received in Application No. 09/194,267, now issued U.S. Patent No. 6,756,054. The Examiner also withdrew: (a) the objection to claim 68; (b) the rejection of claims 22-70 under 35 U.S.C. §112, second paragraph; and (c) the rejection of claims 23-70 under 35 U.S.C. §102(b) or in the alternative §102(a). The Examiner maintained the rejection under 35 U.S.C. §112, first paragraph, for not complying with the enablement requirement.

Claims 23-70 remain pending. No new amendments are made to the claims, and, so therefore, no listing of claims is included in this Response.

ARGUMENTS

The Examiner maintained the rejection of claims 23-70 under 35 U.S.C. §112, first paragraph, for not satisfying the enablement requirement. Applicants traverse this rejection.

Applicants submit that undue experimentation is not required to practice the claimed invention. Contrary to the Examiner's assertions, the specification is replete with working examples. As discussed in Applicants' previous response, the application discloses both *in vitro* and *in vivo* testing using catonic liposomes for gene delivery. The specification discloses *in vivo* testing wherein liposome/plasmid DNA complexes were prepared and intranasally instilled into the lungs of female BALB/c mice. (Page 18, lines 27-32, page 19, lines 1-20). The liposome/plasmid DNA complexes were prepared using either pCF1-βGal plasmid expressing β-galactosidase or pCF1-CAT expressing chloramphenicol acetyl transferase. (Page 24, lines 31-32). Figure 25 presents results from the *in vivo* testing.

The working examples, including both *in vitro* and *in vivo* testing, enable a person skilled in the art to practice the claimed methods. In responding to Applicants' previous

arguments, the Examiner expressed concern that the assays disclosed in the specification determine gene delivery activity and not treatment of cystic fibrosis or other genetic disorders. That is, the Examiner appears to be arguing that the working examples do not provide evidence that the claimed methods work as described. The disclosure does state that the *in vivo* assays, which are reporter gene assays, measured gene delivery activity as a function of chloramphenicol acetyl transferase (CAT) activity or expression. At the time the application was made, however, it was also known in the art to use such reporter gene assays to assess therapeutic potential. For example, an article to Alton et al. (Gene Therapy (2000) 7, 273-278) (attached as Exhibit 1) discloses evaluating therapeutic potential by evaluating CAT expression. Additionally, Alton et al. discloses using a cystic fibrosis reporter gene (pCF1-CAT) similar to that used in the *in vivo* studies disclosed in the present application.

Further, it was known in the art at the time the Application was filed that only a small amount of transgene expression would be needed to provide therapeutic relief in cystic fibrosis. For example, Dorin et al. (Gene Therapy (1996) 3, 797-801) (attached as Exhibit 2)[1] discloses that "modest levels of transgene expression and only partial correction of CFTR channel activity may have a significant clinical impact." (See Gene Therapy (1996) 3, at 797, Abstract).

In response to the Examiner's arguments that "[i]t is unclear the mice are an acceptable model for cystic fibrosis," Applicants submit an article by Boyd et al. (Gene Therapy (2004) 11, 737-738) (attached as Exhibit 3) and an article by Hoffman et al. (Infection and Immunity, Apr. 2005, 2504-2514) (attached as Exhibit 4) that discuss the use of mice models for cystic fibrosis. In discussing mice models as being acceptable for cystic fibrosis, both Boyd et al. and Hoffman et al. reference other articles that predate the U.S. filing date for this application. Applicants submit that these articles demonstrate that mice were and are considered as acceptable models for cystic fibrosis.

The above evidence shows that (1) the application includes numerous working examples, including *in vivo* testing, (2) the *in vivo* testing in the specification measures gene delivery by CAT expression, (3) at the time the application was filed, CAT expression was also known as a way to evaluate therapeutic potential, (4) at the time the application

[1] The abstract in the enclosed copy of the Dorin et al. article is difficult to read, and a separate copy of the abstract is attached at the end of the article.

was filed, it was known that a relatively small amount of gene expression in a cell could have a significant clinical impact and provide therapeutic relief for conditions such as cystic fibrosis, and (5) that mice are acceptable models for cystic fibrosis.

Based on the *in vivo* tests and the knowledge in the art regarding evaluating therapeutic potential and gene expression (e.g., Alton et al.) a person skilled in the art would recognize that the *in vivo* tests demonstrate analyzing or evaluating therapeutic effect using the claimed methods. Additionally, based on the *in vivo* tests disclosed in the specification and the disclosure in Dorin et al. that therapeutic affects can occur with small levels of expression a person skilled in the art would have a reasonable expectation of success in practicing the claimed methods. Thus, the evidence shows that the disclosure enables the claims and would not require undue experimentation.

While Applicants believe that the above evidence sufficiently demonstrates that the application enables the claimed methods, Applicants submit herewith a declaration by Dr. Michael Keller. Dr. Keller has extensive experience in developing non-viral vectors for *in vivo* application. Dr. Keller's declaration includes *in vivo* data demonstrating the transfection ability of a liposome in accordance with the present disclosure (CDAN:DOPE), that was administered intranasally to mice. More importantly, Dr. Keller's declaration demonstrates that a person skilled in the art could, based on the present application, readily ascertain the transfection ability of a liposome/nucleic acid complexes without undue experimentation. Similar to the present Application, Dr. Keller utilized reporter gene assays using a plasmid DNA expressing the CAT reporter gene. Dr. Keller's tests show that liposomes in accordance with the disclosure provide good transfection. At some ratios, the transfection level is comparable to polyethyleneimine but without the severe toxicity problems related to lung inflammation associated with polyethyleneimine.

In view of the evidence in the specification, the state of the art, and Dr. Keller's declaration, Applicants submit that the present application enables a person skilled in the art to practice the claimed invention without undue experimentation. Applicants request that the rejection be withdrawn.

CONCLUSION

For the reasons detailed above, it is respectfully submitted all claims remaining in the application (Claims 23-70) are now in condition for allowance.

Respectfully submitted,

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3/31/06
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Under 37 C.F.R. § 1.8, I certify that this Amendment is being

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